P50

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 37

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ERIC J. MATHUR,
EDWARD J. MARCH
and
WARREN E. SCHOETTLIN

Appeal No. 95-4103
Application 07/919,140[1]

HEARD: MAY 9, 1996

Before WILLIAM F. SMITH, GRON and ELLIS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal from the final rejection of claims 1 through 9. Claims 10 through 21 are pending but have been

[1] Application for patent filed July 23, 1992.

withdrawn from consideration by the examiner under 37 CFR § 1.142(b).

Claims 1, 6, 8 and 9 are illustrative of the subject matter on appeal and read as follows:

1. A purified thermostable DNA ligase from a hyperthermophilic archeabacterium [sic] which catalyzes template-dependent ligation at temperatures of about 30°C to about 80°C, and which substantially retains its catalytic ability when subjected to temperatures of from about 85°C to about 100°C.

6. The ligase of claim 1 wherein said ligase is isolated from an archaebacteria selected from the group consisting of Pyrodictium occultum, Pyrodictium abssyum, Thermodiscus maritumus, Thermococcus celer, Thermococcus litoralis, Thermococcus stetteri, Pyrococcus furiosus, Staphylothermus marinus, Desulfurococcus, Archaeoglobus profundus, Hyperthermus butylicus, Archaeoglobus fulgidus, Pyrococcus strain GB-D, and archabacteria [sic] strains AL-1, AL-2, ES-1 and ES-2.

8. The ligase of claim 1 that is isolated from a recombinant organism transformed with a vector that codes for the expression of said DNA ligase.

9. The ligase of claim 8 wherein said ligase is a Pyrococcus furiosus DNA ligase.

The references relied upon by the examiner in rejecting claims 1 through 9 under 35 U.S.C. § 103 are:

Barany et al. (Barany PCT) WO 91-17237 Nov. 14, 1991

Francis Barany (Barany), "Genetic disease detection and DNA amplification using cloned thermostable ligase," 88 Proc. Natl. Acad. Sci. USA, 189-193 (Jan. 1991)

Frank O. Bryant and Michael W.W. Adams (Bryant), "Characterization of hydrogenase from the Hyperthermophilic Archaebacterium, Pyrococcus furiosus," 264 Journal of Biological Chemistry, no. 9, 5070-5079 (March 1989)

The references cited for the first time in the Examiner's Answer but not relied upon in rejecting claims 1 through 9 under 35 U.S.C. § 103 are:

John M. Ward et al. (Ward), "Phosphocellulose as a tool for rapid purification of DNA-modifying enzymes," 249 Analytica Chimica Acta, no. 1, 195-200 (1991)

Robert C. Tait et al. (Tait), "The rapid purification of T4 DNA ligase from a λT4 lig lysogen," 255 The Journal of Biological Chemistry, no. 3, 813-15 (1980)

Sharon M. Panasenko et al. (Panasenko), "A simple three-step procedure for the large scale purification of DNA ligase from a hybrid λ lysogen constructed in Vitro," 253 The Journal of Biological Chemistry, no. 13, 4590-92 (1978)

Steven B. Zimmerman and Cora J. Levin (Zimmerman), "Deoxyribonucleic acid ligase from nuclei of rat liver," 250 The Journal of Biological Chemistry, no. 1, 149-55 (1975)

Miho Takahashi and Kayoko Tomizawa (Takahashi), "Purification and characterization of DNA ligase II from Drosophila melanogaster," 192 Eur. J. Biochem., no. 3, 735-40 (1990)

Tomas Lindahl (Lindahl), "DNA ligase from rabbit tissues," 21 Methods in Enzymology, Pt. D, 333-338 (1971)

Noboru Oishi and Hiraku Shimada (Oishi), "Purification and properties of a DNA ligase from sea urchin embryos," 95 J. Biochem, no. 4, 1187-1192 (1984)

Serge Hardy et al. (Hardy), "DNA ligase I from Xenopus laevis eggs," 19 Nucleic Acids Research, no. 4, 701-705 (1991)

Claims 1 through 9 stand rejected under 35 U.S.C. § 103 as unpatentable over Barany or Barany PCT each in view of Bryant.

We affirm, but we denominate our affirmance as a new ground of rejection under 37 CFR § 1.196(b).

BACKGROUND

DNA ligases are enzymes which catalyze the formation of phosphodiester linkages between DNA chains and are essential components of the ligase chain reaction (LCR). As explained at page 2, lines 13-26, of the specification:

> LCR is performed by repeated cycles of heat denaturation of a DNA template containing the target sequence, annealing a first set of two adjacent oligonucleotide probes to the target DNA sequence in a unique manner, and a second set of complementary oligonucleotide probes that hybridize to the sequence opposite to the target DNA sequence. Thereafter, a thermostable DNA ligase will covalently link each pair of adjacent probes provided there is complete complementarity at the junction of the two adjacent probes. Because the oligonucleotide products from one round may serve as substrates during the next round, the signal is amplified exponentially, analogous to the polymerase chain reaction (PCR).

Appellants also explain at page 3, lines 8-21 of the specification that:

> DNA ligases exhibiting limited temperature stability have been isolated from Thermus aquaticus (Taq), and from Thermus thermophilus (Tth). See, for example Takahashi et al., J. Biol. Chem., 259:10041-10047 (1984). However, these enzymes do not maintain thermostability at temperatures greater than about 65°C for prolonged periods of up to 10 to 30 minutes as required for typical LCR protocols. Thus, the known DNA ligases are unstable at high temperatures for prolonged periods, and therefore require a "pre-melt" step in LCR

procedures to separate the two strands of the genomic DNA molecule prior to the addition of the enzyme followed by LCR cycles below about 85°C to 90°C.

Appellants discuss the heating conditions necessary for strand separation at page 11 of the specification, indicating that a typical cycle uses a temperature from about 90°C to about 100°C for a time ranging from about 0.5 to 4 minutes. Thus, DNA ligases which retain their catalytic activity after being repeatedly subjected to such high temperature conditions would be very useful in LCR.

Bryant discloses that before the present invention at least 20 species of extremely thermophilic bacteria had been isolated which grow optimally at temperatures above 80°C. All 20 species are archaebacteria and are stated to be remarkable and very distinct from thermophilic eubacteria, e.g., thermophilic eubacteria have lower optimum growth temperatures. Among the 20 species disclosed is Pyrococcus furiosus (T_{opt} 100°C). Bryant states that the discovery of bacteria which grow optimally around 100°C generated considerable interest in the academic and industrial communities and that it could be anticipated that processes would be developed which would take advantage of the thermostable enzymes possessed by these microorganisms.

DISCUSSION

I

Evidence of Obviousness

As stated in Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567, 1 USPQ2d 1593, 1596 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987), "[l]ike all legal conclusions, that under § 103 rests on a factual evidentiary foundation." Thus the determination of the obviousness/nonobviousness of claimed subject matter under this section of the statute is only as sound as its factual evidentiary foundation. Here, the examiner's conclusion of obviousness is based on three prior art references, Barany, Barany PCT and Bryant. See pages 4-5 of the Examiner's Answer. However, in responding to appellants' arguments set forth in the Appeal Brief, the examiner cited the eight new references listed above. In so doing, the examiner did not state that she was making a new ground of rejection under 35 U.S.C. § 103. The procedure followed by the examiner in citing these eight references for the first time in the Examiner's Answer is similar to the procedure used by the Patent and Trademark Office (PTO) which was met with disapproval by the court in In re Hoch, 428 F.2d 1341, 1342, n. 3, 166 USPQ 406, 407, n. 3 (CCPA 1970). The court stated:

> Appellant complains that although neither of [the newly cited references] is mentioned in the statement of either of the appealed rejections and although this fact was pointed out in appellant's brief below, the board approved of their use by the examiner "as suggesting that [appellant's] compounds would exert herbicidal action" and characterizing this as a use in a "minor capacity" (emphasis added) to "further support the rejection." Appellant's complaint seems to be justified, and if we did not find the rejections based solely on Molotsky and the French patent to be sound, we might well feel constrained to reverse the decision of the board. Where a reference is relied on to support a rejection, whether or not in a "minor capacity," there would appear to be no excuse for not positively including the reference in the statement of the rejection.

The eight newly cited references do provide relevant evidence in regard to the level of ordinary skill in this art respecting purification of DNA ligases. Thus the most comprehensive factual evidentiary foundation for a patentability determination under 35 U.S.C. § 103 would be the eleven references cited in the Examiner's Answer, not the three references relied upon in the stated rejection. We recognize that the determination of whether an examiner has made a new ground of rejection in an Examiner's Answer is an administrative matter, reviewable by petition and not subject to appeal. However, whether our affirmance of an examiner's rejection in deciding an appeal under 35 U.S.C. § 134 should be denominated a new ground of rejection under 37 CFR § 1.196(b) is a matter within our jurisdiction. In making this determination, we are guided by the court's agreement

with the appellants in In re Kronig, 539 F.2d 1300, 1302-03, 190 USPQ 425, 426 (CCPA 1976) that

> the ultimate criterion of whether a rejection is considered "new" in a decision by the board is whether appellants have had fair opportunity to react to the thrust of the rejection. We agree with this general proposition, for otherwise appellants could be deprived of the administrative due process rights established by 37 CFR 1.196(b) of the Patent and Trademark Office (footnote omitted).

In Kronig, the examiner relied upon seven prior art references as evidence of obviousness in making a rejection under 35 U.S.C. § 103. In affirming, the board relied upon only three of the seven references. The court determined that the basic thrust of the rejection was the same and that appellants had fair opportunity to react to that rejection.

Here, appellants' first Reply Brief filed September 14, 1994, including appellants' response to the eight newly cited references, was refused entry by the examiner. See the communication mailed December 15, 1994 (Paper No. 25). Appellants' petition (Paper No. 26, February 21, 1995) to have that Reply Brief entered was denied in a Decision on Petition issued by the Group Director of Examining Group 1800 (Paper No. 27, April 5, 1995). A subsequent Reply Brief filed May 5, 1995 (Paper No. 29) limited to the stated new grounds of rejection in the Examiner's Answer under 35 U.S.C. § 112, first and second paragraphs, was

subsequently entered by the examiner and those rejections were withdrawn.

As the case now stands (1) claims 1 through 9 stand rejected under 35 U.S.C. § 103 with Barany, Barany PCT and Bryant used as evidence of obviousness, (2) eight new references have been cited in the Examiner's Answer but are not explicitly relied upon in the statement of the rejection, and (3) appellants have not been able to respond on the record to the citation of the eight new references. We do not see why the patentability of the claimed subject matter under 35 U.S.C. § 103 should be determined on the limited factual evidentiary foundation provided by Barany, Barany PCT and Bryant when the record contains a more comprehensive factual evidentiary foundation, i.e., the eight newly cited references. In other words, spending the resources needed to determine whether the examiner's conclusion of obviousness under 35 U.S.C. § 103 is properly supported by the three references is unwise. Rather, those resources are better spent in determining the patentability of the subject matter presented in this appeal on the basis of the most comprehensive factual evidentiary foundation available, i.e., the eleven references considered together.

Late discovery of relevant evidence in any proceeding can cause procedural discomfort. Be that as it may, appellants are

still entitled to fully and fairly respond to an examiner's action. Here, the examiner's citation of and implicit reliance on eight new references in the Examiner's Answer while at the same time denying that a new ground of rejection has been made and then denying appellants any opportunity to respond to the newly cited references cannot be said to result in appellants' having a "fair opportunity to react to the thrust of the rejection."

Under these circumstances, our consideration of the issues raised under 35 U.S.C. § 103 in this appeal has been based upon the evidence provided by all eleven references cited in the Examiner's Answer. Since we have determined that this evidence supports a conclusion of obviousness under this section of the statute, and appellants have not had a fair opportunity to respond to this rejection, we denominate this affirmance a new ground of rejection under 37 CFR § 1.196(b).

II

We hold that the subject matter of claims 1 through 9 would have been obvious to one of ordinary skill in the art under 35 U.S.C. § 103. As evidence of obviousness, we rely upon Barany, Barany PCT, Bryant, Ward, Tait, Panasenko, Zimmerman, Takahashi, Lindahl, Oishi and Hardy.

We initially note that appellants have argued the patentability of claims 1 through 9 under 35 U.S.C. § 103 on the basis of two separate groups of claims under the then existing provisions of 37 CFR § 1.192(c)(5). The first group of claims is claims 1 through 7 and the second group is claims 8 and 9.

A. Claims 1 through 7

Prima facie case

We will decide the issue of the patentability of the subject matter of claims 1 through 7 under 35 U.S.C. § 103 on the basis of independent claim 1 which has the broadest scope of the claims argued in this group.

Claim 1 is directed to a purified thermostable DNA ligase obtained from a hyperthermophilic archaebacterium. The DNA ligase must catalyze template-dependent ligation at temperatures of about 30°C to about 80°C as well as substantially retaining its catalytic ability when subjected to temperatures of from about 85°C to about 100°C.

At the time of the present invention, various species of hyperthermophilic archaebacteria including Pyrococcus furiosus were known and available to the public. See Bryant and page 13, lines 29-34, of the specification. The thermostability of the enzymes which are found in hyperthermophilic archaebacteria, such

as Pyrococcus furiosus, was also known and appreciated at the time of the present invention. Specifically, having isolated and purified a hydrogenase from Pyrococcus furiosus, Bryant determined that "[t]he hydrogenase was remarkably thermostable since at low concentrations in dilute anaerobic buffer it retained most of its H_2 evolution activity after a 1-h incubation at 100°C" (Bryant, page 5074, right-hand column, first full paragraph). As stated above, Bryant provides evidence that at the time of the present invention workers in this field fully appreciated the advantages possessed by the thermostable enzymes contained in these microorganisms.

The examiner has determined that workers in this field would have understood at the time of the present invention that thermostable microorganisms, such as Pyrococcus furiosus, must contain an active DNA ligase. While appellants argue at page 3 of the Appeal Brief that the examiner has not cited any references that support the position that Pyrococcus furiosus must contain a thermostable DNA ligase, that argument does not take into account that the optimal growing temperature for this microorganism is 100° C. Since the microorganism grows at that temperature and an active DNA ligase is apparently needed for growth, the examiner's determination of the matter rests on a firm, logical, scientific footing.

Appellants acknowledge in the "Background" portion of the specification that at the time of the present invention DNA ligases were an important reagent used in LCR and that thermostability of a DNA ligase used for this purpose was very important.

From these facts, it is reasonable to conclude that at the time of the present invention one of ordinary skill in the art would have understood that (1) Pyrococcus furiosus contains a thermostable DNA ligase which would be active at temperatures up to about 100°C since that is the optimal growth temperature for this microorganism and the hydrogenase isolated by Bryant retained most of its activity at this temperature, and (2) such a thermostable DNA ligase would be useful in LCR since the use of such a thermostable enzyme would allow higher temperatures to be used without inactivating the needed DNA ligase. In other words, at the time of the present invention, one of ordinary skill in the art would have had every reason, suggestion or motivation to isolate a DNA ligase from Pyrococcus furiosus with the full expectation that that enzyme would be active at 100°C and would be useful in LCR.

Thus the issue in this appeal under 35 U.S.C. § 103, as in so many cases in this art area, becomes whether one of ordinary skill in the art at the time of the present invention would have

viewed the isolation and purification of a thermostable DNA ligase from Pyrococcus furiosus as a task which would only have been "obvious to try" or would this hypothetical person approach this task with a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). The resolution of this issue necessarily involves the determination of the level of skill of workers in this field at the time of the present invention in successfully isolating and purifying DNA ligases.

The examiner relies upon Barany and Barany PCT as evidence of the level of skill in the art at the time of the present invention in this regard. In so doing, the examiner has not recognized that Barany is directed to detecting genetic diseases using cloned thermostable ligase which had been previously obtained. As set forth in the "MATERIALS AND METHODS" section of Barany, the thermostable DNA ligase used in that work was purified from E. coli cells as described elsewhere. Thus, Barany, in and of itself, does not provide direct evidence relevant to this issue.

On the other hand, Barany PCT provides such direct evidence. Example VI of Barany PCT describes the purification of DNA ligase from E. coli cells. Of particular interest is the disclosure at

page 55, lines 10-12, where a phosphocellulose column was used in the purification scheme.

Taking a step back and reviewing the three references relied upon by the examiner in stating the rejection, it is an open question as to whether the DNA ligase purification scheme of Barany PCT would have reasonably been expected to isolate and purify a DNA ligase from another cellular source such as the publicly available strains of Pyrococcus furiosus. Barany PCT documents a single successful obtention of a DNA ligase from its host cell. Perhaps the person of ordinary skill in this art would have expected the purification scheme of Barany PCT would allow one to isolate and purify a DNA ligase from Pyrococcus furiosus; perhaps not. The examiner's continued reliance on only the three references does not allow that issue to be easily resolved. However, that is an issue we need not spend any further time considering since more relevant evidence is of record, i.e., the additional eight references newly cited by the examiner in the Answer.

The relevance of these new references to this issue is immediately seen from a consideration of Ward for this reference is entitled "Phosphocellulose as a tool for rapid purification of DNA-modifying enzymes." Ward discloses in the opening paragraph

that molecular biologists in implementing recombinant DNA techniques must use a wide range of DNA-modifying enzymes including DNA ligases. In the paragraph bridging pages 195-196, Ward elaborates, stating that DNA ligases are essential in recombinant DNA experiments and reports that a new technique had been published which requires the use of a thermostable DNA ligase. Ward indicates that this new technique introduces the need for enzymes from thermophilic organisms. Ward provides a relevant summary of the state of the art at the time of the present invention in the first full paragraph of the left-hand column of page 196 stating "[t]he plethora of DNA-modifying enzymes now required by molecular biologists necessitates the use of a generic procedure for purification which is relatively specific for DNA-binding proteins but rapid and capable of coping with many different bacterial extracts." What Ward discovered is that phosphocellulose, a cation exchanger, acts as a pseudo-affinity medium for enzymes that binds the nucleic acids including DNA ligases and provides the needed "generic" purification procedure. DNA ligase is stated at page 198 of Ward to be "[t]he second most important group of enzymes in molecular biology" and that phosphocellulose has been used to isolate DNA ligases from thermophilic bacteria.

Stepping back again, it is apparent that Ward provides a fuller factual background in order to evaluate the isolated

success of Barany PCT in isolating a DNA ligase from E. coli using phosphocellulose. Considering the disclosure of Barany PCT in light of Ward, it can be reasonably concluded that a person having ordinary skill in the art would have expected to isolate many DNA ligases from a variety of microorganisms, including thermophilic microorganisms, using purification schemes based upon phosphocellulose. Whether these four references support a conclusion of prima facie obviousness is again an issue we need not determine since the remaining seven references newly cited by the examiner in the Answer provide yet further relevant evidence.

Takahashi, Lindahl, Oishi, Hardy, Tait, Panasenko and Zimmerman each isolate and purify a DNA ligase using a purification scheme which is premised upon using a phosphocellulose column. Taking yet another step back and considering the evidence provided by all eleven references, the conclusion becomes almost inescapable that at the time of the present invention the hypothetical person of ordinary skill in this art would have well understood that DNA ligases can be isolated from many different cells, including thermophilic microorganisms, using purification schemes premised upon phosphocellulose columns. That many DNA ligases had been purified from a wide variety of cellular sources lends credence to Ward's disclosure of a "generic" method of

isolating and purifying DNA ligases. The fact that the references use different overall schemes to isolate and purify the DNA ligases establishes that the level of skill in this art was sufficiently high that isolating and purifying a DNA ligase from yet another cellular source at the time of the present invention would have been approached with a fair degree of confidence. Thus it is reasonable to conclude from a consideration of all eleven references that one of ordinary skill in the art at the time of the present invention would have found it prima facie obvious to isolate a DNA ligase from Pyrococcus furiosus with a reasonable expectation of success. In re O'Farrell, supra; In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985).

Appellants' Rebuttal

A conclusion of prima facie obviousness, of course, does not end a patentability determination under 35 U.S.C. § 103. As stated in In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986):

> If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984).

Here, the arguments directed to the presence or absence of a prima facie case of obviousness in the Appeal Brief were directed to the examiner's rejection as based upon Barany, Barany PCT and Bryant, not on the evidence provided by the eleven references relied upon by us in reaching our conclusion of prima facie obviousness. Appellants were denied any opportunity to respond to the newly cited references. Thus appellants' arguments are not relevant to the newly stated basis for this rejection.

On the other hand, appellants' arguments directed to the so-called unexpected results obtained from the present invention are relevant. As stated in In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681:

> There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious.

Here, appellants have urged throughout the Appeal Brief that the purified Pyrococcus furiosus DNA ligase of the present invention has several unexpected properties, i.e., a high degree of thermostability, the activity in the presence of ATP and NAD, and a high level of template specificity. See, e.g., page 4 of the Appeal Brief. Conspicuous by its absence in the Appeal Brief, however, is any citation by appellants to objective, factual evidence in this record which establishes that the DNA ligase

obtained by Pyrococcus furiosus does, in fact, have these argued properties. Unexpected results must be established by factual evidence. It has long been held that attorney's argument in a brief cannot take the place of the needed factual evidence. In re Pearson, 494 F.2d 1399, 1405, 181 USPQ 641, 646 (CCPA 1974).

We are aware that certain of the working examples of this application provide data relevant in determining what properties are possessed by the DNA ligase appellants obtain from Pyrococcus furiosus. See, e.g., Examples 8 and 12 of the present specification. However, appellants have eschewed reliance on such data in pursuing this appeal. Evaluation of technical evidence such as this is best left to the examiner in the first instance. That evaluation will have to include the determination of whether the evidence ultimately relied upon by appellants is a comparison with the closest prior art and commensurate in scope with the claims. In re Boesch, 617 F.2d 272, 276-77, 205 USPQ 215, 219-20 (CCPA 1980).[2]

The examiner did not notify appellants that the arguments premised upon so-called unexpected properties were deficient

[2] For example, appellants' arguments are limited to the purported properties of the DNA ligase they isolated from Pyrococcus furiosus, yet claim 1 is of much broader scope.

since they were not supported by objective evidence. As set forth in In re De Blauwe, 736 F.2d 699, 705-06, 222 USPQ 191, 197 (Fed. Cir. 1984), if the examiner had previously pointed this out to appellants, "appellants would, at least, have had notice and would have had an opportunity to file objective evidence" (footnote omitted). The examiner's failure to put appellants on notice as to the lack of objective evidence in support of their argument concerning unexpected properties constitutes a second separate reason to denominate our affirmance of the examiner's decision as a new ground of rejection under 37 CFR § 1.196(b).

B. Claims 8 and 9

Claims 8 and 9 are directed to a purified thermostable DNA ligase as isolated from a recombinant organism and are, in effect, product-by-process claims. It is well settled that the patentability of a product claimed in this manner must be based upon the product itself, not upon the process by which it is made. In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985). Here, appellants have not begun to explain, let alone establish, how a DNA ligase made by the procedures outlined in claims 8 and 9 will differ in any significant respect from a DNA ligase purified from its cellular source. Since the prior

art suggests that thermostable DNA ligase can be readily isolated from hyperthermophilic archaebacteria, such as Pyrococcus furiosus, we hold that the subject matter of claims 8 and 9 would have been obvious from a consideration of the above-listed eleven references. Appellants' arguments concerning unexpected results are adequately answered above.

III

Effect of Bell and Deuel decisions

Appellants relied upon the decision in In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) on pages 9-10 of the Appeal Brief. As understood, appellants made this argument in regard to claims such as 8 and 9 which outline the procedure by which the claimed thermostable DNA ligase is obtained. Since these procedures include the use of nucleotide sequences which code for DNA ligase, appellants appear to believe that the decision in Bell is relevant. We disagree.

As set forth above, claims such as claims 8 and 9 are product-by-process claims. The prior art need not teach or suggest the process set forth in such claims. Rather, the prior art need only teach or suggest the claimed product. Absent appellants establishing in the first instance that the manner of

making the claimed ligase affects the product in any significant respect, we do not find that the Bell decision is relevant in deciding the patentability of these claims under 35 U.S.C. § 103.

In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995), was cited in appellants' communication filed April 21, 1995 (Paper No. 28) requesting this board to remand the application to the examiner or "render a Summary Reversal of the Final Rejections" in view of this decision. The application was remanded to the examiner (Paper No. 30) and a Supplemental Examiner's Answer was issued by the examiner (Paper No. 31). Having considered appellants' position in regard to the relevance of the Deuel decision vis-à-vis the subject matter in this appeal, we, like the examiner, do not find Deuel to be controlling on these facts.

First, the request for a remand is confusing in that in paragraph 2 it refers to "two of the rejections on appeal." The final rejection in this application (Paper No. 14) contained a single rejection of claims 1 through 9 under 35 U.S.C. § 103 as unpatentable over Barany or Barany PCT in view of Bryant. As elaborated in paragraph 5 of the Request, appellants were of the opinion that the examiner had made a second rejection under 35 U.S.C. § 103 directed to claims for polynucleotide sequences encoding a thermostable ligase from the archaebacteria

Pyrococcus furiosus. While claims are pending in this application directed to such subject matter, those claims have not been examined. Rather, they have been withdrawn from consideration under 37 CFR § 1.142(b).

Second, it appears that appellants' position in regard to the decision in Deuel is that Deuel stands for the proposition that it is an error, per se, for an examiner to reject claims under 35 U.S.C. § 103 when any aspect of the rejection relies upon so-called methodology. Since the Deuel decision, the Federal Circuit has spoken to such perceived per se rules stating that substituting "supposed per se rules for the particularized inquiry required by section 103" is legal error. In re Ochiai, 71 F.3d 1565, 1571, 37 USPQ2d 1127, 1132 (Fed. Cir. 1995). See, also, In re Brouwer, 77 F.3d 422, 425-26, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). Thus if prosecution is continued on this subject matter and appellants continue to rely upon cases such as Bell and Deuel, appellants should explain more clearly why the facts in those decisions so parallel the facts in this case that those decisions should be considered determinative of the obviousness inquiry in this case.[3]

[3] An expanded merits panel of this Board has had occasion to determine the relevance of the decisions in Bell and Deuel to claims pending in an ex parte application directed to
(continued...)

Summary

We affirm the decision of the examiner that the subject matter of claims 1 through 9 on appeal would have been obvious to one of ordinary skill in the art under 35 U.S.C. § 103. However, in reaching this conclusion, we rely upon the eleven references cited above. We have also notified appellants for the first time that their arguments directed to unexpected results are unsupported by factual evidence commensurate in scope with their claims. Thus, we denominate this affirmance as a new ground of rejection under 37 CFR § 1.196(b).

Times for response

Any request for reconsideration or modification of this decision by the Board of Patent Appeals and Interferences based upon the same record must be filed within ONE MONTH from the date of the decision (37 CFR § 1.197). Should appellants elect to

[3](...continued)
nucleotide sequences. See Ex parte Goldgaber, Appeal No. 95-2038 (Bd. Pat. App. & Int. 1995). Since this decision is publicly available because the appeal involved a reissue application, we include a copy of the decision in Goldgaber with this decision for appellants' and the examiner's convenience.

have further prosecution before the examiner in response to the new rejection under 37 CFR § 1.196(b) by way of amendment or showing of facts, or both, not previously of record, a shortened statutory period for making such response is hereby set to expire TWO MONTHS from the date of this decision.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED 37 CFR § 1.196(b)

WILLIAM F. SMITH
Administrative Patent Judge

TEDDY S. GRON
Administrative Patent Judge

JOAN ELLIS
Administrative Patent Judge

BOARD OF PATENT
APPEALS AND
INTERFERENCES

Appeal No. 95-4103
Application No. 07/919,140

Finnegan, Henderson, Farabow, Garrett & Dunner, Esq.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Paper No. 23

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DMITRY Y. GOLDGABER, D. CARLETON GAJDUSEK
and MICHAEL LERMAN

Appeal No. 95-2038
Application 07/858,959[1]

ON BRIEF

Before McKELVEY, Chief Administrative Patent Judge, and WINTERS, WILLIAM F. SMITH, GRON, and ELLIS, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal was taken from the examiner's decision refusing to allow claims 2 through 13, which are all of the claims remaining in the application.

THE INVENTION

Appellants' invention relates to cDNA encoding the brain beta-amyloid polypeptide associated with Alzheimer's Disease.

[1] Reissue application filed March 27, 1992, which is seeking to reissue U.S. Patent No. 4,912,206, issued March 27, 1990.

Claim 4, which refers to Figure 1 in the application, is representative of the subject matter on appeal:

4. A clone of DNA which hybridizes to message for beta-amyloid polypeptide of Alzheimer's disease and which hybridizes with the oligonucleotide probe having the nucleotide sequence shown in Figure 1.

FIG. 1

asp ala glu phe arg his asp ser gly tyr
5'- GAI GCI GAI TTI A/C GI CAI GAI T/A C/G I GGI TAI

glu val his his gln lys leu val phe phe
GAI GTI CAI CAI CAI AAI C/T TI GTI TTI T[T] - 3'

ala glu asp val gly ser asn lys

It is apparent that the clone of DNA defined in claim 4 must satisfy these requirements: (1) hybridize to message for beta-amyloid polypeptide of Alzheimer's Disease, and (2) hybridize with the oligonucleotide probe having the nucleotide sequence shown in lines 2 and 4 of Figure 1.

THE REFERENCES

The prior art references cited and relied on by the examiner are:

Glenner et al. (Glenner) 4,666,829 May 19, 1987

Huynh et al. (Huynh), "Constructing and Screening cDNA Libraries in λgt10 and λgt11," DNA Cloning A Practical Approach, Vol. 1, edited by D M Glover, IRL Press, Washington, DC, pp. 49-78 (1985).

THE ISSUE

In the final rejection mailed January 28, 1994, the examiner set forth a number of prior art and non-prior art rejections. Based on a review of the advisory action mailed June 8, 1994, however, we find that all rejections, save one, have been withdrawn. The sole remaining issue is whether the examiner erred in rejecting claims 2 through 13 under 35 USC 103 as unpatentable over the combined disclosures of Glenner and Huynh.

DELIBERATIONS

Our deliberations in this matter have included evaluation and review of the following materials: (1) the instant specification, including Figures 1 through 6, and claim 4 on appeal; (2) appellants' brief before the Board; (3) the examiner's answer; (4) the "Letter to the Board of Patent Appeals and Interferences", with attachment, dated May 19, 1995; and (5) the Glenner and Huynh references cited and relied on by the examiner.

On consideration of the record, including those materials, we find that the examiner did not err in holding that the subject matter sought to be patented would have been obvious at the time the invention was made to a person having ordinary skill in the art based on the combined disclosures of the cited references. Accordingly, we shall sustain the rejection of claims 2 through 13 under 35 USC 103 as unpatentable over the combined disclosures of Glenner and Huynh.

GLENNER AND HUYNH ESTABLISH A PRIMA FACIE CASE OF OBVIOUSNESS

Initially, we note that appellants' brief does not include a statement that the rejected claims do not stand or fall together. See 37 CFR § 1.192(c)(5) entitled "Grouping of Claims". Accordingly, for the purposes of this appeal, the examiner treated all of the appealed claims as standing or falling together and we shall do likewise. Claim 4, which was added to this reissue application by way of amendment, constitutes the broadest claim on appeal. We have, therefore, treated all of the appealed claims as standing or falling together with representative claim 4.

Glenner discloses a purified polypeptide having a molecular weight of about 4,200 Daltons, as determined from gel exclusion column chromatography. The polypeptide is isolated from

cerebrovascular amyloid deposits in patients with Alzheimer's Disease and is referred to by patentee as "the Alzheimer's Amyloid Polypeptide or AAP". In column 3, lines 14 through 40, Glenner discloses the amino acid sequence of that polypeptide. Further, Glenner describes "the gene coding for AAP" and "the DNA or mRNA coding for AAP" in the following context:

> Additionally with the determination of the amino acid sequence of AAP, it is possible to ascertain the base sequence of the gene coding for AAP. A nucleotide probe can be constructed which will recognize and hybridize with the gene so as to provide a further diagnostic test which may determine a genetic predisposition, even in individuals who are not presently synthesizing the polypeptide. Alternatively, a probe can be constructed which recognizes messenger RNA (mRNA) corresponding to the gene and polypeptide. [Emphasis added.]

and

> Having established the amino acid sequence of AAP, a nucleotide probe can be constructed which is complementary to the DNA or mRNA coding for AAP or a portion thereof. Such a probe can then be used as an additional diagnostic test for the disease, or for a predisposition to the disease in individuals who may not express the polypeptide. [Emphasis added.]

See Glenner, column 2, lines 46 through 55, and column 4, lines 30 through 36.

In a series of working examples, Glenner discloses the extraction, purification, and amino acid sequencing of AAP. Further, in Example XIII, patentee provides information and guidelines respecting the synthesis of degenerate oligonucleotide

probes, including a ratio "considered acceptable by those skilled in the art". See column 9, lines 61 and 62. The claims of the Glenner patent cover a substantially purified polypeptide isolated from patients with Alzheimer's Disease, AAP, having the amino acid sequence set forth in column 11, lines 3 through 10. The claims also cover a labelled nucleotide probe, comprising a sequence of nucleic acid substantially complementary to the nucleotide sequence coding for the substantially purified polypeptide isolated from patients with Alzheimer's Disease, AAP, having the amino acid sequence set forth in column 12, lines 42 through 49. Finally, claims 20 and 21 are directed to diagnostic assays using the labelled nucleotide probe.

We believe that the Glenner patent speaks volumes to persons having ordinary skill in the art, and speaks in the chemical languages of both nucleic acids and proteins. It would have been obvious to modify Glenner's teachings by using the degenerate oligonucleotide probes of Example XIII to "pull out" or isolate cDNA encoding the brain beta-amyloid polypeptide associated with Alzheimer's Disease from an adult human brain cDNA library.

First, a person having ordinary skill in the art would have been motivated to isolate cDNA coding for AAP. Isolating the cDNA would enable preparation of copious amounts of AAP for research, study, and the advancement of medical science. In this

regard, it is well known by those skilled in the art of molecular biology that an isolated cDNA can be used to generate copious amounts of the protein which it encodes. Glenner discloses the difficulty of obtaining AAP from autopsies of patients suspected of having Alzheimer's disease. Isolating cDNA which codes for AAP would obviate that difficulty and would enable production of increased quantities of purified AAP for numerous desirable purposes. Merely by way of example, see Glenner, col. 1, lines 60-67; col. 2, lines 38-45; col. 2, lines 56-64; and col. 4, lines 19-29.

Second, Glenner puts a person having ordinary skill in possession of the key to success, i.e., two sets of fully degenerate probes. Again, see Example XIII. Appellants have not controverted Glenner's statement in that example that one nucleotide sequence out of each set of degenerate probes will be perfectly complementary to the DNA sequence coding for the AAP protein. Nor do appellants controvert Glenner's statement that such a ratio "is considered acceptable by those skilled in the art." Glenner is not directed to a layman, but rather to a person having ordinary skill in the art, versed in the field of molecular biology and the use of recombinant DNA techniques. That hypothetical person is presumed to be familiar with technology and techniques in the field of cloning at the time the

invention was made, including (1) rapid advances in the field of cloning discussed in Amgen, Inc. v. Chugai Pharmaceutical Co., 13 USPQ2d 1737, 1753-54 (D. Mass. 1989), and (2) more recent techniques of DNA cloning discussed in the 1985 reference relied on by the examiner, note Chapter 2 authored by Huynh entitled "Constructing and Screening cDNA Libraries in λgt10 and λgt11." We agree with the examiner's finding that it would have been obvious to construct and screen an adult human brain cDNA library using the techniques described by Huynh and two sets of fully degenerate probes prepared in the manner described by Glenner, in order to isolate a cDNA clone meeting the limitations of claim 4 on appeal.

Appellants do not controvert that, at the time the invention was made, it would have been well within the skill of the art to sequence the isolated cDNA rapidly and routinely.

For these reasons, we find that a person having ordinary skill would have sufficient basis for the necessary motivation and predictability of success to here sustain a rejection under 35 USC 103. In a nutshell, the combined disclosures of Glenner and Huynh provide a roadmap which would have directed a person having ordinary skill in the art to isolate DNA encoding the brain beta-amyloid polypeptide associated with Alzheimer's disease. That roadmap, we believe, would have led inevitably to

a clone of DNA meeting the limitations recited in claim 4. On these facts, we hold that the subject matter sought to be patented in claim 4 would have been prima facie obvious within the meaning of 35 USC 103 based on the combined disclosures of Glenner and Huynh.

Appellants argue that Glenner's teachings with respect to oligonucleotide probe synthesis "are strictly prophetic"; that Glenner nowhere discloses an actual probe or its use in isolating the gene encoding AAP; that Glenner merely sets forth a plan for identifying a gene; and that Glenner "puts an idea on the table and that is all". See appellants' brief before the Board, pages 5 through 7. That line of argument is not persuasive in this case.

If, by that argument, appellants mean to say that Glenner is not an anticipatory reference under 35 USC 102, we agree. Glenner does not disclose constructing an adult human brain cDNA library, and screening that library using the degenerate probes described in Example XIII. Nor does Glenner disclose isolating a cDNA clone meeting the limitations of claim 4. The test for obviousness, however, does not require that the claimed invention be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to a person having ordinary skill in the

art. In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Here, the combined teachings of Glenner and Huynh would have suggested appellants' claimed invention.

If, by that argument, appellants would cast aspersions on the Glenner patent or imply that the patent is non-enabling or otherwise discredit its qualifications as a reference, we disagree. As stated in 35 USC 282, a patent shall be presumed valid and each claim of a patent shall be presumed valid independently of the validity of other claims. Here, the Glenner patent is presumed valid and each claim is likewise presumed valid including claims 18 and 19 drawn to a labelled nucleotide probe and claims 20 and 21 directed to using the probe in a diagnostic assay. Considering that presumption of validity, we presume that Glenner's claims are based on a fully enabling disclosure as required by 35 USC 112, first paragraph. See In re Lamberti, 545 F.2d 747, 751 n.2, 192 USPQ 278, 281 n.2 (CCPA 1976); In re Jacobs, 318 F.2d 743, 137 USPQ 888 (CCPA 1963); In re Michalek, 162 F.2d 229, 74 USPQ 107 (CCPA 1947). In view of the statutory presumption of validity, and the detailed information pertaining to oligonucleotide probe synthesis described in Example XIII, appellants have not shown that (1) Glenner fails to put a person having ordinary skill in the art in possession of two sets of fully degenerate probes capable of

hybridizing to a clone of DNA meeting the limitations of claim 4, and (2) the examiner's §103 rejection is based on a non-enabling disclosure. The burden of persuasion falls on appellants to establish that Glenner's disclosure is, in any way, non-enabling and appellants have not met that burden here. Appellants do not and cannot meet that burden by labeling the Glenner disclosure "strictly prophetic." Cf. In re Sivaramakrishnan, 673 F.2d 1383, 1384-85, 213 USPQ 441, 442 (CCPA 1982) (That the Gable patent may not have actually reduced to practice a specific mixture has no bearing on whether that mixture is "described in a printed publication" under 35 USC 102(b)).

We disagree with appellants' statement in the brief before the Board, page 7, that "Glenner puts an idea on the table and that is all". We would suggest that the following metaphor is more apt under the circumstances: "Glenner puts the key in the lock of the door of success". All that remains for a person having ordinary skill is to turn the key and, in so doing, open the lock. That, in our judgment, does not give rise to a patentable invention.

NO REBUTTAL EVIDENCE

Appellants do not present any argument or arguments before the Board based on affidavits, declarations, or other objective

evidence of non-obviousness. Appellants do not rely on evidence which would rebut the statutory presumption that the Glenner patent is valid, or would establish that Glenner's disclosure is non-enabling. Instead, it would appear that appellants incorrectly quote the Glenner patent and misinterpret the evidentiary basis of the rejection. See particularly Glenner, column 2, lines 46 through 48:

> Additionally with the determination of the amino acid sequence of AAP, it is possible to ascertain the base sequence of the gene coding for AAP. [Emphasis added].

Quoting from that portion of the record, but changing the words, appellants state that

> it would be possible to ascertain the base sequence of the gene coding for AAP [emphasis added].

See appellants' brief before the Board, page 5, footnote 1. We find nothing "prophetic" or "would be" about Glenner's disclosure. On the contrary, Glenner discloses clearly and unequivocally that it is possible to ascertain the base sequence of the gene coding for AAP. Glenner further discloses the means for accomplishing that result, i.e., two sets of fully degenerate probes. Glenner further discloses that those probes find successful application in diagnostic assays where the AAP gene must be distinguished from all other DNA present in the human genome. See col. 10, lines 15-54. A person having ordinary skill in the art would have recognized and understood that those

probes may be used successfully to isolate cDNA from a library constructed from mRNA derived from human brain because that library, by definition, contains only those DNA sequences expressed in brain cells. Thus, isolating or "pulling out" a clone which encodes AAP from a suitable cDNA library is less problematical and more likely to succeed than performing a diagnostic assay. Stated another way, Glenner discloses and claims using the probes in diagnostic assays. A fortiori, a person having ordinary skill would have reasonably expected that those probes may be used to isolate cDNA.

BELL AND DEUEL DISTINGUISHED

According to appellants, the examiner improperly relies on methods described by Glenner and Huynh in rejecting the product claims on appeal. Quoting from In re Bell, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993), appellants state that "the issue is the obviousness of the claimed compositions, not of the method by which they are made".

We are mindful of the holding in Bell, and the recently issued opinion In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995), citing Bell with approval and reaffirming the principle that a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the

specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs. We emphasize, however, that each case under 35 USC 103 is decided on its own particular facts. See Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986); In re Cahn, 399 F.2d 236, 158 USPQ 334 (CCPA 1968). Here, unlike the situation presented in Bell or Deuel, "there is something in the prior art to lead to the particular DNA and indicate that it should be prepared". In re Deuel, 51 F.3d at 1558, 34 USPQ2d at 1215. Here, for reasons already presented at length, the combined disclosures of Glenner and Huynh provide a roadmap which would have directed a person having ordinary skill in the art to a DNA clone meeting the limitations recited in claim 4 on appeal. On these facts, we are persuaded that the prior art provides a sufficient basis for the requisite motivation and predictability of success to sustain a rejection under 35 USC 103.

Glenner discloses the amino acid sequence of AAP and two sets of fully degenerate probes and the successful application of those probes in diagnostic assays. This is a different teaching compared with the Rinderknecht references in Bell or the Bohlen reference in Deuel because Glenner, working "back" from protein to gene, begins with the polypeptide AAP and provides ample disclosure leading to the identification of DNA and mRNA which

code for that polypeptide. Conspicuous by its absence from Rinderknecht or Bohlen is any teaching relating to DNA, cDNA, or the gene coding for the polypeptide of interest. Not only is the "primary" reference Glenner more comprehensive than the primary references in Bell or Deuel, but the "secondary" reference Huynh is also stronger than the secondary references in those cases. Huynh evidences a relatively high level of skill in the art of DNA cloning in 1985, specifically Chapter 2 entitled "Constructing and Screening cDNA Libraries in λgt10 and λgt11". Huynh is more recent and more specific with respect to its relevant disclosure compared with the general method for isolating a gene disclosed by Weissman in Bell, or with the general technique for cloning a gene disclosed by Maniatis in Deuel.

It cannot be gainsaid that methodology plays a role in the examiner's rejection. We find nothing intrinsically wrong, however, in the application of methodology in rejecting product claims under 35 USC 103, depending on the particular facts of the case, the manner and context in which methodology applies, and the overall logic of the rejection. Nor do we read Bell or Deuel as issuing a blanket prohibition against the application of methodology in rejecting product claims defining DNA or cDNA. Furthermore, precedent indicates that it is perfectly acceptable

to consider the method by which a compound is made in evaluating the obviousness of the compound. See In re Burt, 356 F.2d 115, 119, 148 USPQ 548, 551-552 (CCPA 1966) (in determining obviousness, it is appropriate to consider such matters as (1) the manner of preparation of the composition vis-à-vis the prior art, (2) the structural similarities as well as differences between the claimed composition and that of the prior art, and (3) the presence or absence of properties which would be unobvious in view of the prior art). Here, Glenner provides motivation to isolate DNA coding for AAP, enabling preparation of copious amounts of the polypeptide by the standard techniques of recombinant DNA. Glenner discloses the means for accomplishing that result, i.e., two sets of fully degenerate probes, and further discloses that those probes find successful application in diagnostic assays. We believe that these facts are distinguishable from Bell or Deuel and that all arrows point in the direction of obviousness. Glenner constructs a "bridge" of information leading from protein to gene and Glenner, in conjunction with Huynh, provides a roadmap leading to appellants' claimed subject matter.

As stated in Deuel, 51 F.3d at 1557, 34 USPQ2d at 1214, the issue presented is

> Whether the combination of a prior art reference teaching a method of gene cloning, together with a

> reference disclosing a partial amino acid sequence of a protein, may render DNA and cDNA molecules encoding the protein prima facie obvious under §103.

Similarly, as stated in Bell, 991 F.2d at 783, 26 USPQ2d at 1531, the issue presented is

> Whether the Board correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning renders the gene prima facie obvious.

The facts before us, however, present a different issue and a more compelling case of obviousness because Glenner discloses more than the amino acid sequence of AAP. Glenner constructs a "bridge" of information leading from the polypeptide AAP via the oligonucleotides corresponding to its amino acid sequence to the gene coding for AAP.

In Deuel, 51 F.3d at 1559, 34 USPQ2d at 1216, the court emphasizes that "obvious to try" is not the standard under 35 USC 103. As stated in In re Eli Lilly and Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990),

> An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

Here, the combined teachings of Glenner and Huynh provide much more than a general disclosure which "may pique the scientist's curiosity". Glenner puts a person having ordinary skill in

possession of two sets of fully degenerate probes, and Huynh discloses specific information pertaining to the construction and screening of a suitable cDNA library. The information in the Glenner patent, when combined with the Huynh reference, provides a reasonable expectation of success which is all that is required for obviousness under 35 USC 103. In re O'Farrell, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

For all these reasons, we find that the particular facts before us are distinguishable from those presented in Bell or Deuel. This case, considered in conjunction with Bell and Deuel, provides a good illustration of the axiom that §103 cases are fact-driven and time-specific. Again, each case under 35 USC 103 must be decided on its own particular facts.

OTHER ISSUES

Appellants' invention involves the beta-amyloid protein of Alzheimer's disease. Appellants state at column 1, lines 11-20, of their patent that this protein is shared with adult Down's syndrome citing, inter alia, Glenner et al., Biochem. Biophys. Res. Commun. 122,1131 (1984). However, the Glenner publication states at page 1133 that beta-amyloid protein of adult Down's syndrome has an identical sequence to the beta-amyloid protein of Alzheimer's disease "with the exception of a substitution of a

Glu for Gln residue at position 11 .... The retention of Gln^{15} strongly suggests that Glu^{11} is a true substitution and is not due to an artificial deamidation." [emphasis added]. The amino acid sequence in Fig. 1 of this application contains Glu at position 11. Per the Glenner publication, the amino acid sequence of Fig. 1 is for the beta-amyloid protein of adult Down's syndrome not Alzheimer's disease as stated by appellants.

Also, it does not appear that the clone of DNA defined in claims 4 through 10, 12 and 13, newly added during this reissue proceeding, finds express or implicit support in the original specification of U.S. Patent No. 4,912,206, especially that portion of the claims that requires the clone of DNA to hybridize with message for beta-amyloid polypeptide of Alzheimer's disease.

Appellants and the examiner should address and clarify these matters if prosecution on this subject matter is resumed in another reissue application. In view of our disposition of this case, however, we refrain from entering new grounds of rejection under the provisions of 37 CFR § 1.196(b).

CONCLUSION

We hold that this case is distinguishable from Bell or Deuel, and that the subject matter sought to be patented in claim 4 would have been obvious based on the combined disclosures of

Glenner and Huynh. As previously indicated, all claims on appeal stand or fall together with claim 4. Accordingly, we sustain the rejection of claims 2 through 13 under 35 USC 103 as unpatentable over the combined disclosures of Glenner and Huynh.

The examiner's decision, refusing to allow claims 2 through 13, is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

FRED E. McKELVEY
Chief Administrative Patent Judge)

SHERMAN D. WINTERS
Administrative Patent Judge) BOARD OF PATENT APPEALS AND INTERFERENCES

JOAN ELLIS
Administrative Patent Judge)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DMITRY Y. GOLDGABER, D. CARLETON GAJDUSEK
and MICHAEL LERMAN

Appeal No. 95-2038
Application 07/858,959[1]

ON BRIEF

WILLIAM F. SMITH, Administrative Patent Judge, concurring,

I agree with the majority's conclusion that the subject matter sought to be patented in this reissue application would have been obvious to a person having ordinary skill in this art at the time the invention was made. I also agree with the majority's reasoning and join its affirmance of the pending rejection under 35 U.S.C. § 103 based upon the combined disclosures of Glenner and Huynh. I write separately to present my views regarding appellants' argument that the decisions in In re

---

[1] Reissue application filed March 27, 1992, which is seeking to reissue U.S. Patent No. 4,912,206, issued March 27, 1990.

Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) and In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) establish a per se rule in deciding the patentability of the nucleotide sequences claimed in this application.

The main argument presented by appellants in this appeal is that the examiner's rejection is in error solely because the present product claims are rejected on the basis of prior art methods. As seen from the dissent, Bell and Deuel can be read as supporting such a per se rule. However, in my view, reading these cases as setting forth a per se rule controlling on the facts in evidence in this record is in error.

Any obviousness determination made under 35 U.S.C. § 103 must begin with the premise that each case must be decided on the facts in evidence in that case. As stated in In re Durden, 763 F.2d 1406, 1410, 226 USPQ 359, 361 (Fed. Cir. 1985): "What we or our predecessors may have said in discussing different fact situations is not to be taken as having universal application." Rather than attempting to extract a mechanical rule from fact driven decisions such as Bell or Deuel, the decision maker should premise the ultimate conclusion of obviousness in a case involving nucleotide sequences, as in any other case, on the factual inquiries set forth in Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966): (1) the scope and content of the

prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

A review of the analogous factual situation presented in In re Kratz, 592 F.2d 1169, 201 USPQ 71 (CCPA 1979), is here instructive. Kratz involved the obviousness of a compound which could be isolated and identified using well established prior art methods. In reversing the decision of the board, the court held that it was error to make weight of the method applicant used in finding the compound because 35 U.S.C. § 103 explicitly states that "[p]atentability shall not be negatived by the manner in which the invention was made." 592 F.2d at 1175, 201 USPQ at 76. Rather, the court indicated that patentability should be based on a comparison of the claimed compound and the "prior art." The court pointed out that the prior art must provide some basis for selecting that compound and stated that the decision maker must distinguish between "substituting skill in the art for statutory prior art . . . and using that skill to interpret prior art." Id.

The court also considered the proscription of 35 U.S.C. § 103 regarding the manner in which an invention is made in Merck & Co. v. Biocraft Laboratories Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847 (Fed. Cir. 1989) stating that the "converse is equally

true: patentability is not imparted where 'the prior art would have suggested that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.' In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)."

In applying the statute to the facts in this case to determine the obviousness of the claimed nucleotide sequences, it appears that the proper context for taking into account the methodology used in the prior art to identify and isolate nucleotide sequences coding for valuable proteins is in the determination of the level of skill in this art. As set forth in Custom Accessories v. Jeffrey-Allan Industries, 807 F.2d 955, 962-63, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986), the determination of the level of skill of the hypothetical ordinary person is primarily based upon real world factors such as "type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of technology; and education level of active workers in the field." Clearly, as applied to this art, the first two stated factors involve the manner in which workers in this field identify and isolate nucleotide sequences when they have knowledge of a partial or complete amino acid sequence of a valuable protein. Thus, the decision maker must determine the level of ordinary skill in this

art from an understanding of how the prior art goes about solving the workaday problem of identifying and isolating nucleotide sequences and then take that level of skill into account when making the legal conclusion of obviousness. 35 U.S.C. § 103; Graham v. John Deere, supra.

The determination of the level of skill in a given art in ex parte patent cases in the PTO is usually based upon the prior art references made of record in that proceeding. As recognized in In re GPAC, ___ F.3d ___, 35 USPQ2d 1116 (Fed. Cir. 1995), "this approach ... offers valuable insight in considering the Custom Accessories factors."[2] Here, real world workers in this field who isolate proteins are clearly "motivated" to determine the nucleotide sequences that code for such proteins so that increased quantities of the protein may be produced through recombinant DNA technology. These real world workers sequence newly isolated proteins and, based upon the determined amino acid sequence, construct a logical family of oligonucleotide probes to

[2] The circumstances of GPAC point out how fact-specific obviousness determinations are and, thus, the danger in trying to extract general or per se rules from reported cases. There, in a first reexamination proceeding this board reversed a rejection under 35 U.S.C. § 103 based solely on an Asbestos reference. In a second, subsequent reexamination proceeding this board affirmed a rejection under 35 U.S.C. § 103 based upon the same Asbestos reference and twelve newly relied upon references, which decision was subsequently affirmed by the court, i.e., different facts--different decision.

screen an appropriate cDNA library. Applying this general method to a specific protein may be more or less difficult depending on the circumstances of that work, e.g. number of unique codons, whether the gene of interest is one in a family of related genes, etc. The desired nucleotide sequence coding for a given protein may be identified and isolated from a cDNA library using only ordinary skill in the art, or in some situations, may require using a greater level of skill. That determination must be made on the facts in a given case and not on the basis of facts in other cases or on the basis of a per se rule.

Using this level of skill in the art to interpret the prior art applied against claim 4, In re Kratz, 592 F.2d at 1175, 201 USPQ at 76, it can be seen that Glenner and Huynh do provide a basis for selecting a nucleotide sequence within the scope of claim 4[3], or as stated in Deuel, 51 F.3d at 1558-59, 34 USPQ2d at 1215, there is "something in the prior art to lead to the particular DNA and indicate that it should be prepared." Specifically, as developed by the majority, Glenner provides a description of a

[3] Claim 4, due to the functional language, is inclusive of a large number of DNA sequences. Appellants have not disputed the underlying basis of the examiner's rejection that using the teachings of Glenner and Huynh in the indicated manner will necessarily result in the identification and isolation of a DNA sequence within the scope of claim 4. Rather, appellants' argument is a legal one that it is per se error for the examiner to rely upon methodology in rejecting the nucleotide sequences of claim 4.

valuable protein and its amino acid sequence. Knowledge of the amino acid sequence allowed Glenner to describe two scientifically and logically sound families of probes. While each family of probes contains 128 members, one member of each family will be perfectly complementary to the DNA sequence coding for the protein. Glenner states at column 9, lines 61-62 that "[s]uch a ratio is considered acceptable by those skilled in the art." Huynh provides textbook details as to how one uses probes such as those described by Glenner to identify and isolate a cDNA sequence of interest from a cDNA library.

In addition, Huynh outlines the standard procedure to be used at page 49 as follows:

> A cDNA library representing the mRNA population is constructed using polyadenylated RNA extracted from the appropriate tissue or cell type. The cDNA clone of interest is then identified within the population of cDNA clones by screening the library with synthetic oligonucleotide probes, cDNA probes representing differentially expressed mRNAs, or an antibody probe. The frequency at which cDNA clones of a particular mRNA species appear in a cDNA library is generally proportional to the abundance of that species in the mRNA population. To isolate cDNA clones of rare mRNAs, it is necessary to be able to construct very large cDNA libraries representative of complex poly(A)$^+$ RNA populations. This chapter presents a simple, detailed procedure for preparing cDNA libraries containing of the order of 10^5 to 10^7 recombinants. Double-stranded cDNAs prepared by this procedure are ligated into one of two λ vectors. The use of a λ vector instead of a plasmid vector makes it possible to take advantage of the high efficiency and reproducibility of *in vitro* packaging of λ DNA as a method of introducing DNA sequences into *E. coli*. The

> high efficiency of cloning cDNAs into λ vectors is useful when cDNA clones of rare mRNAs are sought or when mRNA for preparing is limited in quantity.

Huynh then describes two λ vectors suitable for cloning cDNAs--λgt10 and λgt11. A library based upon either vector can be screened using an appropriate family of oligonucleotide probes (pages 72-73), although it is preferred to screen libraries in λgt11 with antibody probes (pages 73-75).

Appellants admit at column 3, lines 11-13 of the specification of their patent for which reissue is sought that an adult human brain λgt11 cDNA library can be purchased from a commercial source.[4] Since the polypeptide of Glenner is expressed in brain tissue, one of ordinary skill in the art would have expected the

[4] This fact was not relied upon by the examiner in rejecting the pending claims. Rather, the examiner's position is premised upon the ability of one of ordinary skill in the art to construct an appropriate cDNA library based upon the combined disclosures of Glenner and Huynh, i.e., the hypothetical person of ordinary skill would construct a cDNA library when the real world already possessed such a library. I, like the majority, find no error in the examiner's determination of this matter and appellants do not challenge this determination. Why this fact was not relied upon by the examiner and its significance discussed on the record is not apparent. For example, Glenner states at column 2, lines 24-45, that antibodies specific to the protein of interest can be formed. Such antibodies would expectedly be useful in screening the commercial λgt11 adult human brain library since Huynh teaches that it is preferred to screen such libraries using antibody probes. Thus, the level of skill in this art is such that the hypothetical person of ordinary skill would have had, not one, but two methods of probing the commercial λgt11 library to identify and isolate the nucleotide sequence of interest.

cDNA corresponding to the message for this protein to be in the commercial library. As taught by Huynh, λgt11 vector-based cDNA libraries are useful in identifying and isolating cDNA clones of even rare mRNAs. The "motivation" to identify and isolate a nucleotide sequence coding for the valuable protein of Glenner from an appropriate cDNA library is self-evident and has not been denied or controverted by appellants in any manner.

Viewing these prior art facts in light of the level of skill of the ordinary worker in this art, it can be seen that this prior art does provide an objective basis to conclude that the hypothetical ordinary person of skill in this art would have found it obvious to identify and isolate a nucleotide sequence within the scope of claim 4. These facts form a basis to reach the conclusion that it would have been reasonable to expect that the nucleotide sequence of interest was in the commercial human brain λgt11 cDNA library and that one of ordinary skill in this art would have been able to identify and isolate that sequence using either the oligonucleotide probes or the antibody probes described by Glenner.

This is not to create a per se rule the other way, that the obtention of a nucleotide sequence would always be obvious given the amino acid sequence of a protein. It must be kept in mind that this conclusion is only a legal fiction, a so-called prima

facie case of obviousness. Legal fictions must under appropriate circumstances give way to real world facts. Panduit Corp. v. Dennison Manufacturing Co., 774 F.2d 1082, 1095, 227 USPQ 337, 345 (Fed. Cir. 1985) (error not "to credit the real world environment surrounding the inventions" disclosed by applicant and the prior art patents). As stated in In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), "[F]or many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always the possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. [citations omitted]". Here, appellants have not relied upon any objective evidence of nonobviousness which would establish that the obtention of nucleotide sequences within claim 4 on appeal would have required the use of a level of skill beyond the level of ordinary skill in this art.

In summary, rather than try to extract mechanical or per se rules from precedential decisions of our reviewing court or this board, one's efforts would be better spent in making the Graham fact findings including determining the level of skill in the art taking into account the Custom Accessories factors. These cases present very difficult technical and legal issues and are not

amenable to pigeonhole style disposition. It is only by way of very thorough fact finding by the examiner in the first instance, with the aid of applicant, that obviousness determinations can be made at any decisional level with any degree of facility and confidence since a conclusion of obviousness or nonobviousness is only as strong as its factual underpinnings. Based upon the facts in this case, I find no error in the examiner's determination that the subject matter of claim 4 would have been obvious to one of ordinary skill in the art at the time of this invention.

William F. Smith

WILLIAM F. SMITH
Administrative Patent Judge

)
) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DMITRY Y. GOLDGABER, D. CARLETON GAJDUSEK
and MICHAEL LERMAN

Appeal No. 95-2038
Application 07/07/858,959[1]

ON BRIEF

GRON, Administrative Patent Judge, dissenting.

I am led by In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) to conclude that the merits panel's decision to affirm the examiner's rejection under 35 U.S.C. § 103 in this case, based on the comparative records, is inconsistent with the court's direction. Therefore, I am obliged to dissent.

As was the case in Deuel, the claims here are drawn to DNA which encodes a polypeptide responsible for the biological activity of a protein, i.e., the applicants in Deuel claimed DNA

[1] Reissue application filed March 27, 1992, seeking to reissue U.S. Patent 4,912,206, issued March 27, 1990.

encoding a heparin-binding growth factor while the present applicants claim DNA encoding a beta-amyloid polypeptide of Alzheimer's disease. In each case, prior art cited, most especially a reference describing the protein itself, would have motivated a person having ordinary skill in the art to identify and isolate the DNA which encodes production of the protein so to produce increased quantities of the valuable protein via recombinant DNA technology. The prior art of record in Deuel described a unique portion of the amino acid sequence of a valuable protein and provided enough information about the protein along with conventional procedures for analyzing the protein to enable any person skilled in the art to determine the complete amino acid sequence of the protein without undue experimentation. Thus, the prior art cited in each case placed the amino acid sequence of the active polypeptide of a valuable protein in the hands of the public. In each case, general methodologies for (1) identifying target DNA using probes which correspond to the fragment of active polypeptide which has the least possible number of codons, and (2) isolating target DNA so identified, were either described in the cited prior art or known in the art. Thus, in each case, persons having ordinary skill in the art had what the majority of the Board here refers to as a "road map" for, or the "key" to, success in identifying and isolating the target DNA sequence.

The case presented to the court in Deuel included the Board's findings that:

(1) the prior art generally described conventional techniques for identifying and isolating target DNA which encodes a protein from a cDNA library using a reasonable number of DNA probes all of which correspond to an amino acid sequence of a select fragment of the protein;

(2) persons having ordinary skill in the art reasonably would have expected to be able to identify and isolate target DNA which encodes a protein from an appropriate cDNA library using the prior art techniques without undue experimentation; and

(3) persons having ordinary skill in the art would have been motivated by the prior art teaching to identify and isolate the DNA which encodes the protein for use in producing larger quantities of the protein via recombinant DNA technology.

Nowhere in the Deuel decision does the court hold that the Board's findings were clearly erroneous. In Deuel, the Board specifically cited and expressly accepted established views of the state of the art. The Board quoted Watson et al., from Recombinant DNA-A Short Course, Scientific American Books, page 78 (1983):

> [F]or a specific cDNA probe, at worst, only a few weeks may be necessary to screen a phage lambda library for the respective genes . . . [;]

and, from Watson, Molecular Biology of the Gene, Benjamin\ Cummings Publishing Co., page 611 (4th ed. 1987)(emphasis added):

> If . . . the proteins of interest have been characterized by partial or full amino acid sequencing, then . . . intelligent guesses can be made as to its corresponding mRNA (DNA) sequence. Because all amino acids but one are specified by more than one codon . . . it is not possible to go from an amino acid sequence to a DNA sequence unambiguously. By focusing . . . on sequences that mainly contain the less common amino acids, it is usually possible to define a small collection of oligonucleotides, one of which should be exactly complementary to the segment of interest . . . . Such a restricted collection can then be used as probes to identify the complementary cDNA clones by hybridization.

Do the facts in this case differ from the facts in Deuel? They certainly do. However, different facts in different cases are often comparable when cases present similar issues of law. Facts in different cases normally are different. Nevertheless, an earlier decision based on different facts may very well provide valuable legal precedent in deciding a new case with new facts (citations omitted). The better question is whether the record in this case is so different from the record in Deuel that the examiner's rejection of the appealed claims to DNA in this case should be sustained? I think not.

First, I agree with the majority that although the foreign patent publication cited in Deuel (Bohlen) described an active protein which perforce must be encoded by DNA and a unique 19 amino acid N-terminal sequence of that protein, Bohlen (1) did not expressly refer to the DNA which encodes the protein, (2) did not literally express a need or want to identify and isolate the DNA which encodes the protein, and (3) did not point to any specific method known for identifying and isolating DNA

which encodes a protein or assess the potential for success in identifying and isolating the DNA which encodes heparin-binding growth factor using the methods known in the art. Nevertheless, under 35 U.S.C. § 103 a reference must be considered not only for what it expressly teaches, but also for what it would have fairly suggested to persons having ordinary skill in the art. In re Burckel, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979).

In Deuel, the "real world" applicants there (a) defined the DNA they claimed by reference to the complete amino acid sequence of the protein it encodes, (b) defined the protein also claimed by reference to either (i) the amino acid sequence of a unique N-terminal fragment of the protein and its properties or (ii) the complete amino acid sequence of the protein, and (c) traversed the restriction the examiner required between claims drawn to DNA and claims directed to the protein it encodes by arguing that DNA sequences and the proteins they encode are so inextricably related to each other that a search for a DNA sequence would logically include searching for polypeptide sequences. In short, the Board in Deuel found that, when provided with either the complete amino acid sequence of a protein or a unique fragment of the isolated and purified protein, any "real world" person having ordinary skill in the art would have considered the DNA which encodes the protein, would have understood that the DNA which encodes the protein could be employed to produce the protein in large quantities using known recombinant DNA techniques, and

accordingly would have been motivated to identify and isolate the DNA which encodes a valuable protein by methods known in the art.

Second, the majority makes much ado of the fact in this case that the same reference which describes the amino acid sequence of the active polypeptide also mentions the DNA which encodes the polypeptide and teaches that a reasonable number of probes, all corresponding to a fragment of the polypeptide having the lowest number of degenerate codons, can be designed, constructed, and employed to identify and isolate the target DNA by conventional methods with a reasonable expectation of success. However, since the rejection in this case is for obviousness under 35 U.S.C. § 103, I do not see that claimed DNA is any more or less obvious depending on the number of prior art references which supply the requisite teaching. Obviousness under 35 U.S.C. § 103 does not require an express suggestion of the claimed invention in any one or all of the references. The test for obviousness under 35 U.S.C. § 103 is what the combined teachings would have suggested to persons having ordinary skill in the art. In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (Fed. Cir. 1981). Accord In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991)(emphasis added; citations omitted):

> The criterion . . . is not the number of references, but what they would have meant to a person of ordinary skill in the field of the invention. . . .
>
> . . . . .

> . . . [T]he test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention. . . .

Third, although Glenner states that "the polypeptide can be used to produce a nucleotide probe which can hybridize with the gene which codes for this or a homologous polypeptide" (col.1, line 68, to col.2, line 2), Glenner's teaching is no more instructive for or expectant of success than Watson's statements in the textbooks from which the Board in Deuel quoted. Compare the following statement by Glenner (col.2, lines 46-50, emphasis added):

> [W]ith the determination of the amino acid sequence of AAP, it is possible to ascertain the base sequence of the gene encoding for AAP. A nucleotide probe can be constructed which will recognize and hybridize with the gene . . . .

to the 1987 statement by Watson, ibid., quoted by the Board:

> If . . . the proteins of interest have been characterized by partial or full amino acid sequencing, then . . . it is usually possible to define a small collection of oligonucleotides, one of which should be exactly complementary to the segment of interest . . . .

The select amino acid segments of the AAP polypeptide described by Glenner, the corresponding genetic codes of which are sufficiently low in number to generate two sets of 128 different nucleotide probes, are no more specific and no more unique than the N-terminal 19 amino acid segment of the heparin-binding growth factor described by the Bohlen reference applied in Deuel. Both Glenner and Bohlen describe polypeptide segments of proteins from which persons having ordinary skill in the art not only

readily could have designed two sets of 128 DNA probes (see Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-1208 n.4, 18 USPQ2d 1016, 1022 n.4 (Fed. Cir.), cert denied, 112 S.Ct. 169 (1991)) but, as the Maniatis reference in Deuel suggested, likely would have designed two sets of 128 DNA probes for use in combination with even greater expectation of success. In fact, the likelihood of the person having ordinary skill in this art of successfully identifying and isolating the DNA which encodes heparin-binding growth factor with one or a combination of probes based on Bohlen's protein fragment would have been far greater than would have been the case with one or a combination of probes designed from Glenner's polypeptide segment. Glenner states (col.9, lines 59-67):

> . . . One out of the 128 will be perfectly complementary to the DNA sequence coding for the AAP protein. Such a ratio is considered acceptable by those skilled in the art.
>
> To select for the correct coding combination, the hybridization of the probe to the genome conditions can be adjusted to a point where only the perfectly complementary probe will be stably hybridized to the genomic DNA. . . .

The majority finds that persons having ordinary skill in the art would have been likely to succeed in hybridizing Glenner's probes to the target DNA. I agree. However, the likelihood that the skilled artisan would have successfully hybridized probes designed from Bohlen's fragment appears to have been

even greater. Unlike Bohlen's description in Deuel, Glenner does not teach that the polypeptide segments to which his sets of 128 probes correspond are unique to the active polypeptide he describes. Thus, persons having ordinary skill in the art with Glenner's teaching before them reasonably could expect, contrary to the combined prior art teaching in Deuel, that other probes in Glenner's sets of 128 probes would hybridize to some other DNA present in a human genome which includes DNA encoding a host of different polypeptides. To the contrary, only one of 128 probes most likely to have been designed based on Bohlen's unique amino acid sequence reasonably could have been expected to hybridize with genomic DNA. The DNA to which that probe hybridized most likely would be the DNA which encoded heparin-binding growth factor. Although only specific probes from Glenner's sets of 128 could be made to stably hybridize to target DNA, other probes in the sets designed from Glenner's amino acid segments could just as likely stably hybridize to other DNA in the human genome. In short, if a person having ordinary skill in the art reasonably could not have expected to identify and isolate target DNA from a cDNA library using a known method in view of Bohlen's description of a unique N-terminal amino acid fragment of heparin-binding growth factor, the same artisan likely would not have expected to be able to identify and isolate target DNA from genomic DNA by the same methodology in view of Glenner's description of amino acid sequences of the polypeptide of interest to him. If Deuel's

claims are patentable over the prior art cited in that case, it is my view that appellants' claimed DNA must be patentable over the prior art cited in this case.

Fourth, the majority emphasizes the fact that Glenner is a United States patent which presents claims to a labelled nucleotide probe complementary to and hybridizing with DNA which encodes the AAP polypeptide. Claims in a United States patent carry a presumption of validity as a matter of law (35 U.S.C § 282), i.e., the specification of Glenner's patent presumptively would have enabled any person skilled in the art to identify, isolate and use the labelled complementary probe it claims at the time the patent application was filed. Thus, the majority reasons that Glenner presumptively placed a DNA probe complementary to the target DNA appellants claim in the possession of the public. Therefore, the majority reasons, the DNA appellants claim would have been obvious to any person having ordinary skill in the art within the meaning of 35 U.S.C. § 103.

The legal presumption that a description in a prior patent satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph, is not controlling in this case. Certainly, what the PTO allowed in previous cases is not binding in cases presented with different facts and new evidence at another time. In re Willis, 455 F.2d 1060, 1062-1063, 172 USPQ 667, 669 (CCPA 1972). Furthermore, obviousness determinations are generally based on "real world" evidence, not presumptions. Panduit Corp. v.

Dennison Manufacturing Co., 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985) and In re Prater, 415 F.2d 1378, 159 USPQ 583 (CCPA 1968). Absent a more specific description of the precise nucleotide sequence of the probe claimed in Glenner's patent which is complementary to the target DNA, the structure of the target DNA would have been no more obvious to persons having ordinary skill in the art than would have been the case in view of the information either Glenner or Bohlen provides about the amino acid sequences of the protein the target DNA encodes. Thus, the legal presumption should carry no evidentiary weight in this case.

Nevertheless, I generally agree with many of the majority's findings and arguments and even its conclusion that the subject matter claimed would have been obvious to a "real world" person having ordinary skill in the art. However, I am obliged to conclude that the claims on appeal are patentable under 35 U.S.C. § 103 over the prior art cited in this case, as a matter of law.

In my view, the majority misinterprets the legal direction our reviewing court provides in In re Deuel, supra, i.e., the criterion or standards the Patent and Trademark Office (PTO) is thereafter to apply in determining the patentability of claims drawn to DNA which encodes an active polypeptide or protein under 35 U.S.C. § 103. The majority's conclusion that appellants' claimed DNA would have been obvious at the time their invention was made to any person having ordinary skill in the art in view

of the state of the art at that time appears, based on "real world" evidence, to be correct. The problem with the majority's conclusion is that they have erroneously looked to "real world" evidence of patentability under 35 U.S.C. § 103. In the "real world" to which our reviewing court has time and again referred (for example, see Panduit Corp. v. Dennison Manufacturing Co., supra, and In re Prater, supra), knowledge of an unique amino acid sequence of a fragment of a protein, the codon degeneracy of which suggests a reasonable number of DNA probes, and conventional methodology which would have enabled any person skilled in the art to identify and isolate target DNA, reasonably would have placed the DNA sequence which encodes the protein within the public's grasp, i.e., would have reasonably placed the target DNA in the possession of the public. Revisit Glenner's and Watson's statements. Thus, the majority's opinion merely reflects the knowledge in and state of the art as it would have existed in the "real world" at the time appellants' invention was made. However, the court in Deuel directs the PTO to disregard all "real world" reasonable expectations that persons having ordinary skill in this art would have had of successfully identifying and isolating the DNA which encodes a protein, because the standards for obviousness generally applied, even in the biotechnological arts (see In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)), simply are not applicable to

determinations of the patentability of claims drawn to DNA which encodes a protein under 35 U.S.C. § 103.

In my view, the court in Deuel instructed the PTO that claimed DNA which encodes a protein is not prima facie obvious within the meaning of 35 U.S.C. § 103 over prior art teaching unless:

(1) the prior art describes the identical or substantially identical nucleotide sequence of the DNA claimed;

(2) the prior art describes so much of the nucleotide sequence of the claimed DNA that persons having ordinary skill in the art reasonably could have envisioned the sequence and would have been both motivated and enabled to isolate it without undue experimentation; or

(3) the prior art teaches the complete amino acid sequence of the polypeptide or protein and a technique for identifying and isolating DNA which encodes it and the claims are drawn broadly to all DNA likely to encode the protein of interest.

Here, as in Deuel, none of the above three cases is presented. Consequently, the claims on appeal must be patentable under 35 U.S.C. § 103 over the applied prior art. The majority sees "real world" obviousness. So do I. However, the decision of the court in Deuel tells me that evidence of and the standards for "real word" obviousness no longer have a place in determining the patentability of claims drawn to DNA encoding proteins under

35 U.S.C. § 103, regardless of their applicability in other fields of invention.

The opinion of the court in In re Deuel, 51 F.3d at 1558-1560, 34 USPQ2d at 1215-1216, reads:

> [T]he precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules. The redundancy of the genetic code precluded contemplation of the specific cDNA molecules of claims 5 and 7. . . . What cannot be contemplated or conceived cannot be obvious.
>
> . . . . .
>
> The genetic code relationship between proteins and nucleic acids does not overcome the deficiencies of the cited references.
>
> . . . . .
>
> . . . No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.
>
> . . . . .
>
> A different result might pertain, however, if there were prior art, e.g., a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein. See In re Petering, 301 F.2d 676 (CCPA 1962) . . . .
>
> . . . . .
>
> The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. See In re Bell, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993).
>
> . . . . .
>
> . . . [T]he existence of a general method of isolating cDNA or DNA molecules is essentially

> irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.
>
> . . . . .
>
> There must . . . still be prior art that suggests the claimed compound in order for a prima facie case of obviousness to be made out . . . .
>
> . . . . .
>
> . . . The fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious. . . . Thus, a conceived method of preparing some undefined DNA does not define it with the precision necessary to render it obvious over the protein it encodes.[2]
>
> . . . . .
>
> We conclude that, because the applied references do not teach or suggest the claimed cDNA molecules, the final rejection of claims 5 and 7 must be reversed.
>
> . . . . .
>
> . . . Written in . . . result-oriented form, claims 4 and 6 are thus tantamount to the general idea of all genes encoding the protein, all solutions to the problem. Such an idea might have been obvious from the

---

[2] To "envision" a DNA sequence or its chemical structure, the mind of the person having ordinary skill in the art must form a definite and permanent idea of the complete and operative invention. See Bosies v Benedict, ___ F.3d ___, 30 USPQ2d 1862, 1865 (Fed. Cir. 1994); Hybritec Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985). Notwithstanding that definition, the court in O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681, said:

> Obviousness does not require absolute predictability . . . . Indeed, for many inventions that seem quite obvious, there is no absolute predictability . . . . until the invention is reduced to practice.

> complete amino acid sequence of the protein, coupled with knowledge of the genetic code, because this information may have enabled a person of ordinary skill in the art to envision the idea of, and, . . . even identify all members of the claimed genus.

Unlike the majority, I need no further clarification or elaboration of the Bell and Deuel decisions to understand the path the court in Deuel explicitly directs the PTO to take in cases with similar facts and issues. Therefore, I must dissent from the Board's decision in this case. The examiner's rejection of Claims 2-13 under 35 U.S.C. § 103 over the combined teachings of Glenner and Huynh should be reversed in this case as a matter law, even though I completely agree with the majority that the subject matter appellants here seek to patent would have been obvious to a person having ordinary skill in the art in the "real world" of biotechnology, as a matter of fact.

Teddy S. Gron

TEDDY S. GRON
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

Appeal No. 95-2038
Application 07/858,959

Foley & Lardner
Suite 500
3000 K Street, NW
Washington, DC 20007-5109

FORM PTO-892 (REV. 3-78)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER	
NOTICE OF REFERENCES CITED		07/858,959	1800		23
		APPLICANT(S) Doldgaber et al.			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	R	Glesner et al., Biochem. Biophys. Res. Commun. 122 1131 (1984).
	S	
	T	
	U	

Vol. 122, No. 3, 1984 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
August 16, 1984 Pages 1131-1135

ALZHEIMER'S DISEASE AND DOWN'S SYNDROME: SHARING OF A UNIQUE CEREBROVASCULAR AMYLOID FIBRIL PROTEIN

George G. GLENNER, M.D. and Caine W. WONG

University of California, San Diego (M-012), La Jolla, CA 92093

Received June 26, 1984

SUMMARY: The cerebrovascular amyloid protein from a case of adult Down's syndrome was isolated and purified. Amino acid sequence analysis showed it to be homologous to that of the β protein of Alzheimer's disease. This is the first chemical evidence of a relationship between Down's syndrome and Alzheimer's disease. It suggests that Down's syndrome may be a predictable model for Alzheimer's disease. Assuming the β protein is a human gene product, it also suggests that the genetic defect in Alzheimer's disease is localized on chromosome 21.

Neuritic plaques, neurofibrillary tangles and cerebrovascular amyloidosis are the three pathological markers for Alzheimer's disease (1). Cerebrovascular amyloidosis (2) occurs in 92% of all documented Alzheimer's disease cases (3). We recently reported the sequence of a protein (β protein) isolated from cerebrovascular amyloid (4). This β protein appears to be a reliable indicator for the presence of cerebrovascular amyloid and is presumed to be the major amyloid fibril protein. Consequently, the β protein could conceivably serve as a biochemical marker for Alzheimer's disease with a 92% reliability.

A condition which closely simulates Alzheimer's disease is seen in 100% of Down's syndrome individuals over the age of 40 (3). These persons acquire diffuse cerebral dysfunction and/or dementia during life (5,6). Autopsy of such cases reveals all the characteristic lesions found in Alzheimer's disease (3,7). The purpose of the present study was to determine if there is a chemical relationship between the cerebrovascular amyloid fibril protein of Alzheimer's disease and that of adult Down's syndrome. A protein sequence homology between the two would establish evidence that Down's syndrome may be a predictable model for Alzheimer's disease. The results of this study should indicate if it is conceivable that a common genetic defect is shared by both pathological processes.

MATERIALS AND METHODS

Amyloid Fibril Concentration: Human brains of Alzheimer's disease victims obtained at autopsy were frozen at -70° C. Histological sections were taken, stained for amyloid and only those with extensive cerebrovascular amyloidosis were selected for amyloid fibril isolation. The brains of 61 and 62 year old males diagnosed as having Down's syndrome were similarly processed. Age matched normal brains were used for controls. The meninges were stripped, and gross cortex contaminants removed. The tissue was homogenized in 0.09% sodium chloride-0.1% sodium

0006-291X/84 $1.50

azide and the homogenate centrifuged in a Sorvall RC-5B (DuPont Instruments) at 12,500 x g for 60 min. at 4°C. The supernatant was discarded. The resultant pellet was made up of two visually distinct layers. The thin brownish top layer was enriched in amyloid fibrils as monitored by polarization microscopy after Congo red staining. The layers were separated by dissection of the frozen pellet. A second homogenization of the lower layer yielded a significant second crop of amyloid fibrils. The amyloid enriched top layer was homogenized in 0.05 M TRIS-HCl, 3 mM NaN_3, 0.01 mM $CaCl_2$, pH 7.5 buffer to make an approximate 4% solution (w/v). Solid collagenase (EC 3.4.24.3 Sigma Chemical type I) was added in a 1:100 ratio (weight enzyme: weight pellet) and the resultant mixture was incubated in a Dubnoff shaker bath at 37° for 8 hrs. The digestion by collagenase was monitored by Congo red staining with polarization microscopy. After the digestion was completed, the mixture was centrifuged in a Beckman L-5-50B ultra-centrifuge at 105,000 x g for 60 min. at 4°C. The supernatant was discarded and the pellet frozen at -20°C.

Protein Extraction: The collagenase-treated pellet was solubilized in 6 M guanidine-HCl, 0.1 M TRIS-HCl, 24 mM dithiothreitol, 0.34 mM EDTA, pH 8.0 (22% w/v) and stirred at room temperature for 48 hrs. After 48 hrs. the solution was centrifuged in a Beckman L-5-50B ultracentrifuge at 105,000 x g for 60 min. at 4°C. The pellet was separated from the supernatant. The supernatant was placed into 1000 molecular wt. cut off dialysis tubing (Spectra/Por 6, Fisher Scientific) and dialyzed, lyophilized and the resulting powder stored dessicated at -70°C.

G-100 Sephadex Column Chromatography: The procedure was identical to that employed previously (8) using a 2.5 x 100 cm G-100 calibrated Sephadex column (Pharmacia) equilibrated with 5 M guanidine-HCl, 1 N acetic acid. The column was calibrated with cytochrome C (horse heart), 12,384 M_r and glucagon, 3,485 M_r. The protein elution profile was monitored at 280 nm with a Beckman 35 spectrophotometer. The protein peak centered at 4,200 M_r was pooled and dialyzed against deionized water, lyophilized and stored dessicated at -70°C.

High Performance Liquid Chromatography (HPLC): One hundred μg of the lyophilized protein from peak fractions of the Sephadex column was solubilized into 25 μl of 5 M guanidine-HCl, 1 N acetic acid. This was injected into a Waters HPLC system. The mobile phase was: solvent A: 0.1% trifluoroacetic acid/H_2O, solvent B: 100% acetonitrile. The gradient was linear from 10% to 50% solvent B over 60 min. Flow rate was 0.8ml/min. and the protein peaks were detected at 229 nm with 2.0 AUFS. The stationary phase was a Vydac 214TP54 C_4 peptide column. Three major protein peaks were found that had no correspondence with control samples: one at 35% solvent B and the others at about 36% solvent B. These protein peaks were pooled separately, lyophilized and stored at -70°C.

Amino Acid Sequencing: HPLC purified samples were dissolved in heptafluorobutyric acid and loaded in a Beckman 890 C spinning cup sequencer. The collected anilothiazolone amino acids were converted to phenylthiohydantoin amino acids (PTH-amino acids) with 1 N HCl/MeOH at 50°C for 10 min. The PTH-amino acids were dried and redissolved in MeOH. The PTH-amino acids were analyzed on a Beckman 322 HPLC system fitted with an ETH-Permaphase guard column and an IBM 6 μ CN column in line. The eluent was monitored at 254 nm.

RESULTS AND DISCUSSION

These studies reveal the HPLC elution profiles of the β protein from the cerebrovascular amyloid fibrils of Alzheimer's disease and adult Down's syndrome are almost identical (Fig. 1). The Down's profile revealed a lesser quantity of the β_1 peak. No corresponding peaks were noted in three control preparations. In addition these chromatographs resolved from both protein preparations a β_3 peak, previously obscured within that of β_2 (4). It has been shown that the β_1 and β_2 proteins were homologous by amino acid sequence analysis (4). Since β_3 was initially included in β_2 but did not result in sequencing background, β_3 is assumed to be homologous to β_2. Why β protein appears as a doublet or triplet on HPLC is presently unknown. The

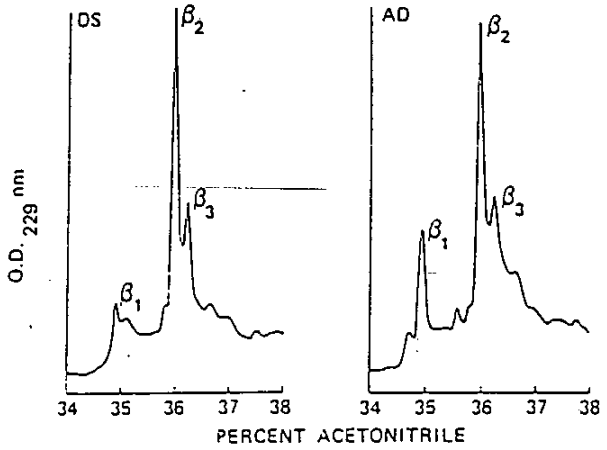

Fig. 1 HPLC of the cerebrovascular amyloid fibril β protein from an Alzheimer's disease patient (AD) previously isolated on Sephadex G-100, as compared to the β protein of an adult Down's syndrome individual (DS) demonstrating three major protein peaks (β_1, β_2 and β_3). The β_1 and β_3 proteins have identical amino-terminal amino acid sequences (4), while the characteristics of β_2 are presently unknown (See text).

amino acid sequence analysis of the Down's β_2 protein fraction to residue 24 is presented in Table 1. This protein was found to have an amino acid sequence identical to that of the Alzheimer's disease β_2 protein (4) through position 24 with the exception of a substitution of a Glu for Gln residue at position 11 (Table 1). The retention of Gln^{15} strongly suggests that Glu^{11} is a true substitution and is not due to an artifactual deamidation. The β_2 protein is not homologous to the serum protein gamma trace (9) found to compose the cerebrovascular amyloid protein of an Icelandic hereditary amyloid angiopathy (10) nor to any other known sequenced protein (4). The preparation from the second Down's case gave an HPLC profile with an identical major peak at 36% acetonitrile, but inadequate material was available for sequencing.

TABLE 1. Automated amino acid sequence analyses of β_2 protein to position 24 from cerebrovascular amyloid fibrils obtained from adult Down's syndrome (DS) and Alzheimer's disease (AD). Variant residue is underlined.

	1	2	3	4	5	6	7	8	9	10	11	12
DS	Asp	Ala	Glu	Phe	Arg	His	Asp	Ser	Gly	Tyr	Glu	Val
AD	Asp	Ala	Glu	Phe	Arg	His	Asp	Ser	Gly	Tyr	Gln	Val
	13	14	15	16	17	18	19	20	21	22	23	24
DS	His	His	Gln	Lys	Leu	Val	Phe	Phe	Ala	Glu	Asp	Val
AD	His	His	Gln	Lys	Leu	Val	Phe	Phe	Ala	Glu	Asp	Val

These findings indicate that of the three disease processes most often characterized by cerebrovascular amyloidosis, i.e., Alzheimer's disease (1,3), adult Down's syndrome (3) and hereditary Icelandic amyloid angiopathy (10), only Alzheimer's disease and adult Down's syndrome share an homologous amyloid protein. This is the first chemical evidence of a relationship between Alzheimer's disease and Down's syndrome.

There is presently no known spontaneous or experimental animal model for Alzheimer's disease. There are mouse models for Down's syndrome (11), but since the trisomic fetuses do not survive beyond term, their value for the study of Alzheimer's disease is limited. The human familial cases of Alzheimer's disease tend to follow an autosomal dominant pattern of inheritance (12) with the usual statistical prediction of affected progeny. However, the great similarity in the cerebral lesions between adult Down's syndrome and Alzheimer's disease (3,7) and the demonstration of chemical homology in the pathologic amyloid fibril β protein strongly suggests that Down's syndrome may represent the first truly predictable model for Alzheimer's disease (as discussed below).

No specific diagnostic test for Alzheimer's disease short of brain biopsy is presently available during the patient's life. The presence of amyloid fibril deposits in vessel walls is indicative of fibrillar derivation from an abnormal serum protein. Several examples can be cited. This has been shown for amyloid fibrils derived from the light polypeptide chain of an immunoglobulin protein (13), a prealbumin (Met^{30}) variant (14) and an SAA protein idiotype (15). Therefore, we anticipate that a protein antigenically related to β protein will be detectable in the serum of individuals with Alzheimer's disease and in those with adult Down's syndrome. This should lead to a specific blood serum test (e.g. radioimmunoassay) for the diagnosis of Alzheimer's disease based on the presence of a serum protein sharing antigenic determinants with β protein. Furthermore, Down's syndrome individuals may provide a diagnostic pattern of serum β protein concentration levels during aging that might be predictive of eventual diffuse cerebral dysfunction and/or dementia (5,6). Such a pattern might lead to a better understanding of the pathogenetic cerebral process common to both Alzheimer's disease and Down's syndrome (3), and help to detect individuals at risk for Alzheimer's disease.

Assuming β protein is a human gene product, the presence of a common amyloid protein in both Down's syndrome (trisomy 21) and Alzheimer's disease suggests the possibility that the genetic defect in Alzheimer's disease (whether acquired or heritable) is localized to chromosome 21. This makes possible alternative approaches to the non-invasive diagnosis of Alzheimer's disease (16,17).

ACKNOWLEDGMENTS

We wish to express our appreciation to Karen Rasmussen for technical assistance, to Fred Hill of the UCSD Weingart Protein Sequence Facility for the amino acid sequence determina-

tions, to Dr. Jack Kyte for the use of the HPLC system and to Dr. Russell Doolittle for the computerized search for amino acid sequence homologies. We also wish to express our special gratitude to Drs. R.M. Peterson and H.L. Wolfinger, Jr., of the San Diego Regional Center for the Developmentally Disabled for making possible the autopsy acquisition of the Down's syndrome tissue. This study was supported by a grant from the Weingart Foundation and a contribution from the National Alzheimer's Disease and Related Disorders Association and the Hoffman-La Roche Foundation.

REFERENCES

1. Glenner, G.G. (1983) *Arch. Pathol. Lab. Med.* 107, 218-282.
2. Glenner, G.G. (1980) *New Eng. J. Med.* 302, 1283-1291, 1333-1343.
3. Glenner, G.G. (1983) *Banbury Report 15: Biological Aspects of Alzheimer's Disease.* Cold Spring Harbor Symposium, 137-144.
4. Glenner, G.G. and Wong, C. (1984) *Biochem. Biophys. Res. Comm.* 120, 885-890.
5. Jarvis, G.A. (1984) *Am. J. Psychiatry* 105, 102-106.
6. Owens, D., Dawson, J.C., Losin, S. (1971) *Am. J. Ment. Defic.* 75, 606-612.
7. Ellis, W.G., McCulloch, J.R., and Corley, C.L. (1974) *Neurology* 24, 101-106.
8. Glenner, G.G., Harada, M., and Isersky, C. (1972) *Prep. Biochem.* 2, 39-51.
9. Lofberg, H., Grubb, A.O., Sveger, T., and Olsson, J.E. (1980) *J. Neurol.* 23, 159-170.
10. Cohen, D.E., Feiner, H., Jensson, O., Frangione, B. (1983) *J. Exp. Med.* 158, 623-628.
11. Epstein, C.J. (1983) *Banbury Report 15: Biological Aspects of Alzheimer's Disease.* Cold Spring Harbor Symposium, 169-182.
12. Heston, L.L. (1976) *Science* 196, 322-323.
13. Glenner, G.G., Terry, W., Harada, M., Isersky, C., and Page, D. (1971) *Science* 172, 1150-1151.
14. Dwulet, F.E. and Benson, M.D. (1984) *Proc. Natl. Acad. Sci. USA* 81, 694-698.
15. Hoffman, J., Ericsson, L.H., Eriksen, N., Walsh, K.A., Benditt, E.P. (1984) *J. Exp. Med.* 159, 641-646.
16. Maniatus, T., Fritsch, E.F., and Sambrook, J. (1982) *Molecular Cloning: A Laboratory Manual.* Cold Spring Harbor New York Press, pp. 545.
17. Gusella, J.F., Wexler, N.S., Conneally, P.M., et al. (1983) *Science* 306, 234-238.

Paper No. 25

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DMITRY Y. GOLDGABER, D. CARLETON GAJDUSEK
and MICHAEL LERMAN

Appeal No. 95-2038
Application 07/858,959[1]

ON BRIEF

Before WINTERS and WILLIAM F. SMITH, Administrative Patent Judges, McKELVEY, Senior Administrative Patent Judge, and GRON and ELLIS, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

ON REQUEST FOR RECONSIDERATION

Appellants request reconsideration of the Board's decision mailed September 6, 1995, affirming the rejection of claims 2 through 13 under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Glenner and Huynh.

[1] Reissue application filed March 27, 1992, which is seeking to reissue U.S. Patent No. 4,912,206, issued March 27, 1990.

The request is predicated on appellants' belief that "they have been unduly prejudiced by their decision not to argue the separate patentability of the claims" on appeal. According to appellants, their decision not to argue separate patentability was made before the court entered its opinion and decision in In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995). Appellants argue that their "perspective" would have been different if they had the benefit of Deuel when they filed their Brief before the Board, "because it is clear that claims of varying scope may be treated differently under an In re Deuel analysis." See the Request for Reconsideration, page 2. Appellants state that where isolated DNA is claimed in structural terms, i.e., by reciting a specific DNA sequence, Deuel focuses attention on the obviousness of the claimed compositions, not of the method by which they are made. See the Request for Reconsideration, paragraph bridging pages 2 and 3. Citing Deuel, appellants ask that we now consider claims 2 and 3 separately. The argument lacks merit.

Initially, we remind appellants of this argument presented in the Brief before the Board, page 4:

> Although the Examiner cites method-related teachings in the art, Appellants again emphasize that claims 2-13 are not directed to methods, they are directed to products. The Examiner's prior art methods do not suggest the claimed DNA products because "the issue is the obviousness of the claimed compositions, not of the method by which they are made." In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993). The cited

> methods therefore simply do not support a prima facie case of obviousness as a matter of law [emphasis in original].

Appellants complain that they did not have the benefit of Deuel when they filed their Brief. Nonetheless, appellants had the benefit of In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and presented argument based on Bell, focusing on the difference between claimed compositions drawn to specific DNA sequences and general cloning techniques for preparing DNA. See the above-quoted portion of appellants' Brief before the Board, and see the Board majority's original opinion under the section entitled "Bell and Deuel Distinguished." Where, as here, Deuel reaffirms principles set forth in Bell respecting the patentability of claimed DNA, we find little merit in appellants' position. In filing their Brief before the Board, appellants chose not to argue any claim or claims separately and presented argument centering on structural obviousness and the Bell opinion. Deuel issued after appellants filed their Brief, and Deuel adheres to the principles of structural obviousness enunciated in Bell. Those facts do not provide a rational basis entitling appellants to reconsideration on the merits of claims 2 and 3.

We next refer to the rules governing practice and procedure before the Board when appellants filed their Brief. Specifically, see 37 CFR § 1.192(c)(5) (1994) which reads as follows:

> (5) Grouping of claims. For each ground of rejection which appellant contests and which applies to more than one claim, it will be presumed that the rejected claims stand or fall together unless a statement is included that the rejected claims do not stand or fall together, and in the appropriate part or parts of the argument under subparagraph (c)(6) of this section appellant presents reasons as to why appellant considers the rejected claims to be separately patentable.

As the Board majority stated in its original opinion, appellants' Brief does not include a statement that the rejected claims do not stand or fall together. Accordingly, for the purposes of this appeal, the examiner treated all of the appealed claims as standing or falling together and we have done likewise. Claim 4, which was added to this reissue application by way of amendment, constitutes the broadest claim on appeal. We have, therefore, treated all of the appealed claims as standing or falling together with representative claim 4, and this is entirely appropriate under the above-quoted rule.

We disagree with appellants' argument in the Request for Reconsideration, page 3, that the Board considered only claim 4 in reaching its decision; that the Board's opinion avoids the structural obviousness issue raised in Deuel; and that the Board evades the full force of Deuel. As explained in the immediately preceding paragraph, the Board confined its analysis to claim 4

because appellants chose not to group or argue any claims separately in presenting their case on appeal. Appellants' suggestion that the Board "avoided" or "evaded" the issues raised in Deuel is frivolous.

We invite attention to appellants' "Letter to the Board of Patent Appeals and Interferences" filed May 19, 1995, Paper No. 22 in the file wrapper.[2] As stated by appellants, this letter is submitted "to draw the Board's attention to the attached Federal Circuit decision, In re Thomas F. Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995)." In the ensuing pages, appellants argue why Deuel is relevant to the disposition of this appeal and compels a holding of non-obviousness. Conspicuous by its absence from this letter, however, is any grouping of claims or statement that the rejected claims do not stand or fall together or explanation why, in light of Deuel, appellants consider the rejected claims to be separately patentable. Appellants do not group or argue any claim or claims separately, either in their Brief before the Board or in the letter filed May 19, 1995.

[2] The Board considered this paper in its original deliberations. See the Board majority's opinion, section entitled "Deliberations."

Appellants have not been "unduly prejudiced" by their own decision not to argue the separate patentability of claims, before and after the court entered its opinion in Deuel. Appellants elected not to argue claims separately under the relevant rules of practice, even in light of Deuel. Accordingly, they are not due separate consideration of claims 2 and 3.

Appellants' "perspective" respecting the separate patentability of claims did not change on entry of the court's opinion in Deuel, as can be seen from a review of Paper No. 22, filed May 19, 1995. We suspect that appellants' "perspective" changed on receipt of the Board's decision, sustaining the rejection of claims 2 through 13 under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Glenner and Huynh. Belatedly, appellants want to argue claims 2 and 3 separately, but this they cannot do. A new argument advanced in a petition for reconsideration, but not advanced in appellants' Brief or Reply Brief, is not properly before the Board and will not be considered. See In re Kroekel, 803 F.2d 705, 709, 231 USPQ 640, 642-43 (Fed. Cir. 1986).

Finally, in their Request for Reconsideration, appellants do not point to any error in the Board's analysis on the merits with respect to representative claim 4.

For these reasons, the Request for Reconsideration is denied.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

DENIED

SHERMAN D. WINTERS
Administrative Patent Judge

WILLIAM F. SMITH
Administrative Patent Judge

FRED E. McKELVEY
Senior Administrative Patent Judge

TEDDY S. GRON
Administrative Patent Judge

JOAN ELLIS
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

Foley & Lardner
3000 K St., N.W.
Suite 500
Washington, DC 20007-5109